PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference CDK2146	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/05544	International filing date *(day/month/year)* 18.12.2003	Priority date *(day/month/year)* 24.12.2002
International Patent Classification (IPC) or both national classification and IPC C07F9/24		
Applicant RHODIA CONSUMER SPECIALTIES LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23.07.2004	03.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Elliott, A Telephone No. +49 89 2399-8218

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/05544

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-5 as originally filed

Claims, Numbers

1-16 received on 23.12.2004 with letter of 20.12.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/05544

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 17-19

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 17-19

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13
	No:	Claims	14
Inventive step (IS)	Yes:	Claims	1-13
	No:	Claims	14
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	-

2. Citations and explanations

   see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

The application relates to a process for producing a phosphorodiamidite by reacting a phosphorus trihalide with a dialkylamine in a polar solvent to form an intermediate and subsequently reacting the intermediate with a hydroxyalkyl compound and a dialkyl amine in the presence of a non-polar co-solvent. Also claimed is the use of the phosphorodiamidite prepared by the above method in the synthesis of oligonucleotides.

The following documents are referred to in this report:

D1: WO 03/106468 A (RHODIA) 24 December 2003 (2003-12-24)
D2: WO 03/087130 A (ISIS PHARMACEUTICALS INC (US)) 23 October 2003 (2003-10-23)
D3: PATENT ABSTRACTS OF JAPAN vol. 012, no. 075 (C-480), 9 March 1988 (1988-03-09) & JP 62 212395 A (NIPPON ZEON CO LTD), 18 September 1987 (1987-09-18)
D4: HAMAMOTO S TAKAKU H: 'New Approach to the Synthesis of Deoxyribonucleoside Phosphoramidite Derivatives' CHEMISTRY LETTERS, CHEMICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 8, 1986, pages 1401-1404, XP002902766 ISSN: 0366-7022
D5: PFLEIDERER W ET AL: 'Inhibition of HIV-1 replication and activation of RNase L by phosphorothioate/ phosphodiester 2',5'-oligoadenylate derivatives' JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 270, no. 11, 17 March 1995 (1995-03-17), pages 5963-5978, XP002079044 ISSN: 0021-9258
D6: HOUALLA D ET AL: 'PREPARATIONS ET QUELQUES PROPRIETES DE COMPOSES CONTENANT LA LIAISON PHOSPHORE TRIVALENT-AZOTE' BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE, SOCIETE FRANCAISE DE CHIMIE. PARIS, FR, 1965, pages 2368-2373, XP009028565 ISSN: 0037-8968
D7: 'FLUKA CHEMIKA, BIOCHEMIKA UND ANALYTIKA KATALOG 1997/98' 1997 , FLUKA CHEMIE AG XP002277275

III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

No opinion is given as to the patentability of claims **15** and **16**, these claims corresponding to original claims 18 and 19 for which no search report was drawn up (the claims make reference to the examples).

V Reasoned statement under Art 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

The subject-matter of claims **1-13** would appear to be novel in the light of the prior art as none of the prior art documents discloses the use of two different non-miscible solvents for the different steps of the presently-claimed process. D3 describes the reaction between a phosphorus trihalide and a secondary amine and the subsequent reaction of the bisaminomonohalogenophosphine with an alcohol (no details of the solvent system used are given in the abstract for D3). D4 discloses the reaction of PCl_3 with diisopropylamine in ether to firstly produce bis(diisopropylamine)chlorophosphine

which is further reacted again in ether with 2-pyridylethanol. D5 exemplifies the more typical synthesis wherein PCl_3 is first reacted with the alcohol and then with the amine (cf. the preparation of compound (3) in column 1 on page 5964 and the synthesis of compound (27) in column 1 on page 5966). D6 in the experimental part thereof (page 2370, columns 1 & 2) shows firstly the preparation of tris(dialkylamino)phosphines and then their reaction with an alcohol to produce the phosphorodiamidites.

On the other hand the subject-matter of amended claim **14** (which corresponds to claim 16 as originally filed) would not appear to be new. It should firstly be pointed out that a compound prepared by a different synthetic route to that employed in the past is still the same compound. Document D7 which is an extract from Fluka's chemicals, biochemicals and analytical reagents catalogue from 1997/1998 contains reference to the specific compound of original claim 15 and even states its use as being for nucleotide synthesis (cf. references cited in D7). On the basis of D7 alone claim 14 lacks novelty. It should further be added that, although the process of claims 1-13 would appear to produce a purer product than achieved with prior art syntheses, the fact that the products from these prior art syntheses would have been further purified before their use means that a product of the same purity as that presently achieved was clearly known in the art - it follows that a lack of unity objection could also be raised as the subject-matter of claims 1-13 is no longer linked to the subject-matter of claim 14 by means of the fact that the compounds prepared in claims 1-13 are known.

Claims **1-13** would, on the basis of the fact that the process provides a purer product compared with the prior art processes, appear to be based on inventive merit.

Claim **14**, lacking novelty, correspondingly lacks inventive step.

Other matters:

1. The applicant has not cited any prior art in the application. D3-D6 should therefore be mentioned in the description (Rule 5.1(a)(ii) PCT).

2. **Certain documents cited**

D1, a PCT application published after the filing date of the present application, is not to

be considered as prior art according to Rule 64.3 PCT.

D1 is an application providing a method for producing cyanoalkyl tetraalkylphosphoramidites by reacting phosphorus trihalide with a cyano-containing agent to form cyanoalkylphosphordihalidite which is reacted with a dialkylamine to form the cyanoalkyl tetraalkylphosphoramidite and amine hydrochloride byproduct at least a portion of which is in the form of a precipitate. The amine precipitate is removed by filtration and the filtrate is further treated with a substance capable of removing any dissolved amine hydrohalide.

D2, published in the priority interval of the present application, is likewise not to be considered as prior art according to Rule 64.3 PCT.

D2 provides a process for purifying a phosphorodiamidite by solvent extraction.

Neither D1 nor D2 would appear to affect the positive opinion expressed above concerning claims 1-13.

CLAIMS

1. A method of phosphorodiamidite production which method comprises the steps of reacting a phosphorus trihalide with a dialkyl amine in a polar solvent to form an intermediate compound and subsequently reacting the intermediate compound with a hydroxyalkyl compound and a dialkyl amine, in the presence of a non-polar co-solvent.

2. A method as claimed in Claim 1 in which the phosphorus trihalide is phosphorus trichloride.

3. A method as claimed in Claim 1 in which the phosphorus trihalide is phosphorus tribromide.

4. A method according to any one of Claims 1 to 3 in which the dialkyl amine is diisopropylamine.

5. A method as claimed in any one of Claims 1 to 3 in which the dialkyl amine is selected from the group consisting of dimethylamine, diethylamine, di-n-propylamine, di-n-butylamine, di-isobutylamine or di-tert-butylamine.

6. A method as claimed in any one of the preceding claims in which the polar solvent is a nitrile compound.

7. A method as claimed in Claim 6 in which the nitrile compound is acetonitrile.

8. A method as claimed in Claim 6 in which the polar solvent is propionitrile or benzonitrile.

9. A method as claimed in any one of the preceding claims in which the hydroxyalkyl compound is hydroxypropionitrile.

10. A method as claimed in any one of Claims 1 to 8 in which the hydroxyalkyl compound is methanol or tert-butyl alcohol.

11. A method as claimed in any one of Claims 1 to 10 in which the alkane co-solvent is a C_5 to C_9 aliphatic hydrocarbon.

12. A method as claimed in any one of Claims 1 to 10 in which the alkane co-solvent is an alicyclic hydrocarbon.

13. A method according to any one of the preceding claims in which the ratio of polar solvent to non-polar solvent is 1:1.

14. The use of a compound as made by the method of claim 1 in the synthesis of oligonucleotides.

15. A method of phosphorodiamidite production, substantially as hereinbefore described with reference to the Examples.

16. The use of a phosphorodiamidite compound, substantially as hereinbefore described with reference to the Examples.